Original Article

Depicting and comparing the time to normalize "erythrocyte sedimentation rate" following two combination therapies in rheumatoid arthritis patients: a randomized clinical trial

Sasan Fallahi (MD) [1, 2]
Abdolrahman Rostamian (MD) [*3]
Ali Khalvat (MD) [3]
Zahra Khazaeipour (MSC) [4]
Fatemeh Shahbazi (MSC) [4, 5]

1-Department of Rheumatology, Shafa Hospital, Kerman University of Medical Sciences, Kerman, Iran.
2-Rheumatology Research Center, Tehran University of Medical Sciences, Tehran, Iran.
3-Department of Rheumatology, Valiasr Hospital, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran.
4-Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran.
5-Department of Biology, Payame Noor University, Karaj Unit, Karaj, Iran.

***Correspondence:** Abdolrahman Rostamian, Department of Rheumatology, Valiasr Hospital, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran.
Postal code: 1419733141

E-mail:
arostamian@sina.tums.ac.ir
Tel: 0098 21 66911294
Fax: 0098 21 66911294

Received: 6 Sep 2012
Revised: 1 Oct 2012
Accepted: 2 Dec 2012

Abstract

Background: Erythrocyte sedimentation rate (ESR) is one of the predictors of improvement in handling rheumatoid arthritis. This study was designed to define and compare the time of achieving normal ESR and also the percentage for the normalization of this marker at several points of time in two different combination therapies.

Methods: Fifty-two rheumatoid arthritis patients randomly received methotrexate, chloroquine, prednisolone (MCP) or azathioprine, chloroquine, prednisolone (ACP) and all were followed up for 34 weeks. Chloroquine and azathioprine were given, 150 mg/d and 2 mg/kg/d, respectively. Methotrexate was given, 0.2 mg/kg/week and simultaneously increased 2.5 mg monthly if no clinical response was seen. Prednisolone was started, 0.3 mg/kg/d and tapered after one week. ESR at baseline and during follow-up were checked. The data were collected and analyzed. This clinical trial was registered in the Iranian Registry of Clinical Trials (www.irct.ir) with registration number ID: 2012110611383N1.

Results: The percentages of obtaining normal ESR after 2nd, 4th, 6th, 8th, 18th, 34th weeks of follow up were 42.4%, 53.9%, 57.7%, 65.4%, 88.5%, 96.2% in the MCP group and 47.9%, 65.3%, 74%, 78.3%, 82.7%, 87% in the ACP group. The mean time of obtaining normal ESR was 9.15 (95%CI, 5.58 to 12.73) weeks in MCP group and 9.04 (4.04 to 14.05) weeks in the ACP group ($p>0.05$).

Conclusion: The results show that the time to achieve normal ESR and percentage of its normalization were almost the same in both treated groups.

Keywords: Rheumatoid arthritis, Inflammation, Methotrexate, Azathioprine, Prednisolone.

Caspian J Intern Med 2013; 4(1): 564-568

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by synovitis, joint damage and progressive disability in high percentage of patients. It is well known that the inhibition of inflammation, joint effusion and obtaining normal erythrocyte sedimentation rate (ESR) in early phase of disease result in good outcome such as reducing ligament damage, subchondral bone erosions and disability in RA patients (1). Methotrexate (MTX) is one of the drugs with high rate of continuation in RA treatment (2). Besides its toxicity, it seems that MTX has better effect than most biological agents (3). For the early and intensive treatment, a combination of disease modified anti-rheumatic drugs (DMARDs) may be required to accomplish some effects and setting target values as a standard way to treat RA today (4). One way to treat the RA patients is to use the combination of DMARDs or immunosuppressors with the use of short period of prednisolone to help induce remission of active RA and tapering it after achieving a visible clinical response (5-9). Erythrocyte sedimentation rate (ESR) is one of the components of improvement criteria for handling RA (7, 8).

ESR is an element in the original disease activity score (DAS) or in the modified version of the disease activity score with 28-joint count (mDAS28) (9, 10). It can be measured simply and further deterioration of joints is less likely to occur when this marker is consistently controlled (11). Time to normalize ESR for the different combination therapies has not been much studied. The goal of this study was to evaluate the time for achieving normal ESR in two groups of combination therapies: metotherexate-chloroquine-prednisolone (MCP) and azathioprine-chloroquine-prednisolone (ACP). We were also interested in depicting the percentage of obtaining normal ESR at different time points of follow up (2nd, 4th, 6th, 8th, 18th, 34th weeks) in these two groups.

Finally, it would be defined which treatment protocol was superior to another one, considering the time to normalize ESR and percentage of achieving normal ESR for two different drug regimens.

Methods

A total of 52 cases with RA from Rheumatology Clinic of Imam Khomeini Hospital in Tehran were recruited in a single blind randomized clinical trial study. Patient selection was performed during 17 months. The inclusion criteria were age >18 years, fulfilling the criteria of the American College of Rheumatology for RA 1987, active RA which specified by ESR ≥20 in males and ESR ≥30 in females, morning stiffness >30 min and ≥3 joints involved in physical examination (12).

The exclusion criteria were stage IV disease, previous combination therapy with the same medication like this study, liver or renal failure, pregnancy, active or chronic infection, anemia, ophthalmic complications of chloroquine during follow up, patients with irregular visits (the patients who were not seen on defined follow-up time) and the patients without drug compliance or with special medical complications such as rise of serum creatinine. The sample size for each group was an estimate of 26 cases based on a difference of 0.3 between these two groups. The α and β errors chosen for these calculations were 0.05 and 0.20, respectively. The sample size calculation was 52 participants, a total of 26 patients in each group. The 52 patients were allocated randomly in two parallel study groups. One group (26 patients) was treated with MCP and the other one (26 patients) with ACP. Azathioprine (AZT) and chloroquine were prescribed with 2 mg/kg/d and 150 mg daily, respectively. Metotherexate (MTX) was started with 0.2 mg/kg weekly and increased 2.5 mg monthly if no response was obtained (maximum dose, 0.3 mg/kg/week). Prednisolone was started with 0.3 mg/kg/d, tapered 2.5 mg weekly to a maintenance dose, 0.1 mg/kg/d and continued with the same dose. The osteoporotic patients diagnosed by bone mass densitometry (BMD) were treated with alendronate 70 mg/week. In both groups dairy products were recommended to be consumed. Each patient was followed up for 34 weeks in multiple sessions (2nd, 4th, 6th, 8th, 18th and 34th week).

A checklist was used for data collection and filled in each visit separately. The contents of checklist were the patients' profiles (age, sex, education level), duration of disease, history of smoking, osteoporosis, rheumatoid factor (RF) (only in the first visit), erosion in hand X-ray (only in the first visit), tender and swollen joints and lab data, including white blood cell, (WBC), ESR, creatinine, liver function test, and patient group (MCP or ACP). The physical exam of the patients was performed by a physician who was unaware of the kind of medications (single blindness).

Pain and global assessment of physician and patient was measured by 0-10 scale. Normal ESR was defined as ESR<30 in females and ESR<20mm/h in males and measured with Westergren method in the same central laboratory for reasons of uniformity (8). The outcome variables (end points) were achieving normal ESR (%) at different points of time (2nd, 4th, 6th, 8th, 18th, 34th week follow-up) and also the mean time of acquiring normal ESR for both groups, separately. All of the patients gave informed consent and the study protocol was ethically approved by Tehran University of Medical Sciences.

Statistical Analysis: All data were analyzed by SPSS version 11.5. The difference in duration of disease and number of involved joints and also mean changes of ESR before and after intervention were compared between the MCP and ACP treated groups using independent sample t-test. The comparison of RF positivity between the 2 groups was performed by Fisher exact test. Difference in erosion was also analyzed by chi-square test.

The percentage of achieving normal ESR after 2nd, 4th, 6th, 8th, 18th and 34th week were calculated by Kaplan Meier method and the statistical difference between the two groups was analyzed with log rank test. A p-value of <0.05 was considered statistically significant. We performed

sensitivity analysis for comparing the results of ESR between the 2 groups by considering the different presumptive conditions (best and worst).

Results

The MCP and ACP treated groups each with 26 cases were enrolled in the study. Three patients in ACP treated group were missed out on the study, because they were seen only in one session and therefore, no follow up was done. There was not any missing case in MCP treated group.

All of the other patients were maintained from the beginning up to the end of study (34 weeks later) and switching from one treatment group to another did not happen in any of the cases. The minimum and maximum duration of disease in our selected patients were exactly the same in both groups 2 months and 10 years, respectively. The demographic data of patients at the beginning of the study are shown in table 1. There was no significant difference in RF positivity, erosion in hand joints and number of involved joints between the two groups (p>0.05) (table 1 and 2).

Table 1. Demographic data of patients in two groups at the beginning of study

Characteristics	MCP* group	ACP** group
Age (year) (mean±SE)	53±3.24	52.17±3.38
Sex		
Male, N (%)	4 (15.4)	8 (34.8)
Female, N (%)	22 (84.6)	15 (65.2)
Smoking, N (%)	5 (19.2)	5 (21.7)
RF+♦, N (%)	22 (84.6)	14 (60.9)
Joint erosion, N (%)	8 (30.8)	8 (34.8)
Osteoporosis, N (%)	11 (42.3)	8 (34.8)
Duration of disease (month) (mean±SE)	33.61±7.35	29.47±7.8

* Methotrexate,Chloroquine, Prednisolone, **Azathioprine, Chloroquine, Prednisolone,♦ Rheumatoid Factor

The mean of ESR levels (mm/ 1 hour) in the follow-up of the two assigned groups at the beginning of study and at the 2nd, 4th, 6th, 8th, 18th, 34th week follow up were 56.1, 34.3, 29.3, 24.3, 17.9, 17, 16.1 in MCP treated group and 47.8, 31.3, 26.3, 21.5, 23.1, 19.1, 18.7 in ACP treated group, respectively. The survival analysis with Kaplan Meier method verified that the percentage of achieving normal ESR after 2nd, 4th, 6th, 8th,18th, 34th week follow up is 42.4%, 53.9%, 57.7%, 65.4%, 88.5%, 96.2% in MCP treated group and 47.9%, 65.3%, 74%, 78.3%, 82.7%, 87% in ACP treated group. The mean time of achieving normal ESR in MCP treated group was 9.15 (5.58 to 12.73, CI: 95%) weeks and 9.04 (4.04 to 14.05, CI: 95%) weeks in ACP treated group. The difference in time to normalize ESR between the two groups was not significant by log rank test (p>0.05) (figure 1). We performed sensitivity analysis to compare the results of ESR between the 2 groups by considering the different presumptive conditions (best and worst) of the 3 missed cases through a follow up. Sensitivity analysis by considering each of the presumptive conditions showed that the absence of significant difference between MCP and ACP treated groups was maintained furthermore. Therefore, it seems that the time to achieve normal ESR and percentage of obtaining normal ESR is almost the same for two treatment protocols. Also, the mean changes of ESR from baseline to the time of last examination were compared between both groups. The mean decrease included 39.96±3.64 and 29.05±2.62 in MCP and ACP treated group, respectively with significant difference between them (p<0.0001). In some patients, ESR re-increased during tapering of prednisolone and therefore, led to the increase of prednisolone dosage and re-tapering after response appeared. This occurred in 20.8% of MCP and 31.6% of ACP treated groups with no statistically significant difference between them (p>0.05). No complication was seen in any of the study groups.

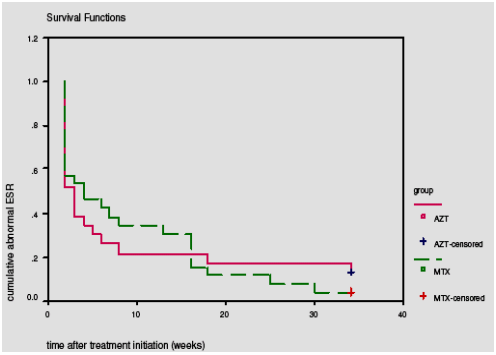

Figure 1. Kaplan Meier method was used to define achieving normal ESR in MTX and AZT-treated group during 34 weeks after treatment initiation. Log rank test was used for comparison between two study groups (p>0.05).

Table 2. Clinical data of patients in two groups at the beginning and the end of study

	MCP*		ACP**	
	Before (mean±SE)	After (mean±SE)	Before (mean±SE)	After (mean±SE)
Swollen joints count	9.92±0.67	0.69±0.23	9.95±0.76	1.3±0.26
Tender joints count	11.81±1.12	0.70±0.21	11.85±1.34	1.2±0.25
Global assessment				
Patient (0-10 scale)	6.2±1.1	1.8±0.6	6±1.2	1.7±0.5
Physician (0-10 scale)	5.8±1.1	1.5±0.4	6.1±0.9	1.4±0.4
Pain (0-10 scale)	5.6±1.2	1.5±0.4	5.3±1.1	1.7±0.6
ESR£(mm in 1st hour)	56.07±5.65	16.11±2.01	47.78±5.46	18.73±2.84

* Methotrexate,Chloroquine, Prednisolone ** Azathioprine, Chloroquine, Prednisolone £ Erythrocyte sedimentation rate

Discussion

The ESR results have role on the RA patient's diagnosis and follow-up. Specifically, the length of time taken for the ESR value to return to the normal rate is one of the factors that show the reduction of disease activity and remission. In RA patients, sometimes the high ESR value is associated with the high level of disease activity. The ESR value has recently become one of the RA classification criteria (American College of Rheumatology/European League against rheumatism collaborative initiative) (13, 14). Therefore, the ESR value and its time taken to return to the normal rate may have an important role in the diagnosis and monitoring RA activity. Paying attention to the results of the present survey was indicative of similarity between the mean time of obtaining normal ESR between MCP and ACP treated groups (with the strategy used in this study). We got the average time of achieving normal ESR in the 8th and 9th week respectively in both groups. The percentage of obtaining normal ESR was also depicted very similarly for both groups. All clinical characteristics of the patients before treatment such as swollen joints counts and joint erosions were almost the same for the two study groups (table 1and 2). Therefore, those features could not be responsible for the obtained result by comparing the two types of intervention. However, it should be noted that more significant decrease of ESR from baseline to last examination was seen in MCP than the ACP treated group. Limited studies were found about the time of obtaining normal ESR in different protocols for handling RA patients.

Our results are compatible with Hamdy et al. and Poormoghim et al. studies (15, 16). They did not reveal any differences between ESR and remission in MCP and ACP treated groups after 24 weeks in Hamdy study and 48 weeks in Poormoghim research. However, clinical response was faster in MCP than ACP treated group in Poormoghim et al. study. Also the time of obtaining normal ESR and the percentage of achieving normal ESR in different time points has not been defined in their studies.

In comparison with our study, Darmawan et al. have reported that the time of obtaining normal ESR with step down bridge combination of 5 immunosuppressors drugs (intravenous and oral) is about 14 days (17). The shorter time for ESR normalization in Darmawan et al. study in comparison with our study is due to simultaneous use of the different and additional immunosuppressors that include cyclophosphamide, myvophenolate mofetil, cyclosporine, MTX and corticosteroid in Darmawan protocol. Focusing on the other results of our study clarifies that the normalization of ESR has not been sustained in all patients.

This could be in part due to latency in appearance of the effects of MTX and AZT which resulted in the increase of ESR after tapering prednisolone in the first weeks and re-normalization of ESR in later weeks. Anyway, after 18 weeks, the majority of patients (about 85%) have acquired stabilized normal value of ESR (figure1). We had 3 missed out cases that might have affected the results. In order to resolve this problem, sensitivity analysis was performed for comparing the results between the 2 groups; however, the absence of significant difference between MTX and AZT-treated group was maintained. Small sample size appeared to be a limitation in this survey. Implementing other investigations with larger sample size and also, with other combination therapies are suggested.

The new information which was presented in this survey was the estimation of the average expected time to normalize ESR for the two kinds of combination therapies with particular protocol and dosage applied to the RA patients.

Acknowledgments

We thank the RA patients in helping us perform this clinical study.

Funding: This study was a part of internal medicine residency thesis which was supported by Rheumatology Department, Valiasr Hospital, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences.
Conflict of interest: None.

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